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The Epidemiology and Pathogenesis of Neoplasia in the Small Intestine

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Abstract

PURPOSE: The mucosa of the small intestine encompasses about 90% of the luminal surface area of the digestive system, but only 2% of the total annual gastrointestinal cancer incidence in the United States.

METHODS: The remarkable contrast in age-standardized cancer incidence between the small and large intestine has been reviewed with respect to the cell type patterns, demographic features, and molecular characteristics of neoplasms.

RESULTS: Particularly noteworthy is the predominance of adenocarcinoma in the colon, which exceeds 98% of the total incidence by cell type, in contrast to that of 30% to 40% in the small intestine, resulting in an age-standardized ratio of rates exceeding 50-fold. The prevalence of adenomas and carcinomas is most prominent in the duodenum and proximal jejunum. The positive correlation in global incidence rates of small and large intestinal neoplasms and the reciprocal increases in risk of second primary adenocarcinomas suggest that there are common environmental risk factors. The pathophysiology of Crohn inflammatory bowel disease and the elevated risk of adenocarcinoma demonstrate the significance of the impaired integrity of the mucosal barrier and of aberrant immune responses to luminal indigenous and potentially pathogenic microorganisms.

CONCLUSION: In advancing a putative mechanism for the contrasting mucosal susceptibilities of the small and large intestine, substantial differences are underscored in the diverse taxonomy, concentration and metabolic activity of anaerobic organisms, rate of intestinal transit, changing pH, and the enterohepatic recycling and metabolism of bile acids. Experimental and epidemiologic studies are cited that suggest that the changing microecology, particularly in the colon, is associated with enhanced metabolic activation of ingested and endogenously formed procarcinogenic substrates.

Keywords

Cancer Epidemiology; Molecular Biology; Neuroendocrine Tumor; Adenocarcinoma; Non-Hodgkin Lymphoma; Gastrointestinal Stromal Tumor; Crohn Disease; Celiac Disease; Microbial Flora; Bile Acid Metabolism

INTRODUCTION

Neoplasms of the small intestine are rare throughout the world. Global incidence is generally less than 1.0 per 100,000, ranging from 0.3 to 2.0 per 100,000, when age-standardized to the world population. In the United States, cancers of the small intestine represent 0.4% of total cancer cases and 0.2% of cancer deaths (1). The small intestine, an elongated tube consisting of the duodenum, jejunum and ileum, represents 75% of the length (i.e., about 5–6 meters), extending from the pylorus to the ileocecal valve, and 90% of the absorptive surface area of the esophago-gastrointestinal system. Remarkably only 2% of the total annual cancer incidence of the digestive system occurs in the small intestine. In contrast, approximately 57% of cancers in the digestive system are diagnosed each year in the large intestine, which measures about 1.5 meters in length.

The average annual age-adjusted incidence per 100,000 for cancer of the small intestine, when age-standardized to the U.S. 2000 population, is 1.9 in men, and 1.4 in women. From 1975 to 2000, the rates increased by almost 50%. This trend reflected increases for adenocarcinomas, malignant carcinoid tumors, and lymphomas in men, and for carcinoid tumors and lymphomas in women (2). The age-specific incidence increases for carcinoid tumors, adenocarcinomas, and lymphomas after age 30, whereas the incidence of sarcomas seems to level off after age 70. The incidence of carcinoid tumors and adenocarcinomas are slightly higher in blacks compared with whites, and the reverse is true for lymphomas and sarcomas (3). Adenocarcinomas are most common in the duodenum and proximal jejunum, whereas lymphomas and carcinoid tumors predominate in the ileum and distal jejunum (4). The international incidence of adenocarcinoma of the small intestine is positively correlated with the distribution of colon cancer incidence. The pattern of increased risk of second primary cancers of the small and of the large intestine suggest similar causal mechanisms, rather than the effects of surveillance bias or the carcinogenic effects of treatment of the index primary cancer (5, 6). The U.S. Surveillance, Epidemiology and End Results (SEER) cohort of male and female patients who had survived 5 or more years after the diagnosis of cancer of the small intestine, experienced more than a two-fold increase in risk (risk ratio [RR] = 2.62; 95% confidence interval [CI] = 1.77, 3.75) of colon cancer. Similarly, the cohort of patients with colon cancer exhibited an increased risk (RR = 3.44; 95% CI = 3.00, 3.95) of cancer of the small intestine (7). The reciprocal increases in risks were amplified in subcohorts in whom the index primary cancer was diagnosed before 60 years of age, suggesting interactions with genetic susceptibility factors (8). The increases in risk of second primary colorectal cancer have been described in association with a prior diagnosis of adenocarcinoma or carcinoid tumor in the small intestine (9–11).

MORPHOLOGY AND MOLECULAR CHARACTERISTICS OF ENTERIC NEOPLASMS

The mucosal layer of the small intestine is replaced in 4–7 days (12) and consists of absorptive, glandular, and neuroendocrine cells that line the crypts and villi. The crypt epithelium functions in cell proliferation and cell renewal. Pluripotential stem cells are located at the base of each crypt, from which undifferentiated reserve cells migrate toward the lumen and differentiate into absorptive cells or enterocytes, or into mucin-secreting

goblet cells, before undergoing apoptosis (13, 14). The villi are mucosal folds of columnar epithelial cells that amplify the absorptive surface area of the intestinal lumen. The tunica mucosa of the villi rests on a basement membrane, lamina propria, and muscularis mucosa. The lamina propria contains lymphocytes, macrophages, and plasma cells. The plasma cells secrete the immunoglobulin IgA that diffuses into the intestinal lumen or lamina propria. Mucosa-associated lymphoid cells are scattered throughout the mucosa of the small intestine, and in the ileum aggregate as macroscopic Peyer patches. Antigens that gain access to mucosal macrophages and Peyer patches activate B and T lymphocytes that function in antigen processing and immunosurveillance.

Neuroendocrine Tumors

Carcinoid tumors or argentaffinomas of the gastrointestinal tract are neuroendocrine tumors, derived from enterochromaffin or Kulchitsky cells that are capable of producing serotonin (5-hydroxytryptamine). Neuroendocrine tumors comprise a heterogeneous group of neoplasms that exhibit distinctive morphologic and biologic features. Such tumors originate from pancreatic islet cells, gastro-enteric tissues, gall bladder and biliary duct system, respiratory epithelium, and thyroid parafollicular cells (15, 16). The neuroendocrine cells are capable of producing various polypeptide hormones, including serotonin, gastrin, histamine, insulin, glucagon, vasoactive intestinal peptide, calcitonin and somatostatin. Endocrine secretion is regulated by G protein-coupled receptors, ion-gated receptors, and receptors with tyrosine kinase activity (17). Gastrointestinal neuroendocrine tumors may be classified according to their embryologic origin into tumors of the foregut (bronchopulmonary, stomach, pancreas, duodenum), midgut (jejunum, ileum, appendix, right colon), and hind gut (left colon, rectum). The classification "neuroendocrine" is derived from their functional relationships to multipotential stem cells that are associated with the secretion of marker proteins such as neurokinin A, chromogranin A, synaptophysin, and urinary 5-hydroxy indoleacetic acid. Neuroendocrine tumors of the mediastinum and of gastro-duodenopancreatic cells may be associated with the hereditary multiple endocrine neoplasia (MEN) syndrome (type-1), von-Hippel-Lindau disease, neurofibromatosis (type-1), hereditary nonpolyposis colorectal cancer, and tuberous sclerosis. The type-1 MEN syndrome is an autosomal dominant disorder with phenotypic features of multifocal parathyroid tumors, adenomas of the anterior pituitary, pancreatic and duodenal neuroendocrine tumors, and carcinoma of the thymus gland (18).

Within the small intestine, neuroendocrine carcinoid tumors occur predominately in the ileum, and rarely in the duodenum. In the duodenum, these tumors are classified as gastrinomas. In the SEER population, the average annual age-adjusted incidence per 1,000,000 based on the 1973–2005 registration for carcinoid tumors of the small intestine was 7.7 (white men), 5.5 (white women), 14.4 (black men), and 8.7 (black women). The incidence per 1,000,000 for carcinoid tumors of the colon was 2.7 (white men), 3.2 (white women), 4.7 (black men), and 4.0 (black women) (Table 1). Over the past 30 years, the SEER registries have documented a 400% increase in the age-adjusted incidence of carcinoid tumors of the small intestine (19). Carcinoid tumors accounted for 42% of the total of small intestinal tumors. In histopathologic studies based on surgical and autopsied patients with carcinoid tumors of the small intestine, up to one-third of cases were multifocal.

Molecular studies of sporadic gastroenteropancreatic neuroendocrine tumors have demonstrated that chromosomal instability, copy number aberrations, point mutations, methylation abnormalities, and ablation of putative tumor-suppressor pathways are associated with neoplastic transformation and tumor progression. The prominent mutations associated with intestinal adenocarcinomas (e.g., TP53, K-*ras*, p16, APC and DCC alleles) are not salient molecular events in the pathogenesis of gastrointestinal neuroendocrine

tumors (20, 21). Comparative genomic hybridization, loss of heterozygosity, and mutational analyses suggest genetic pathways that are selectively involved in the pathogenesis of gastrointestinal neuroendocrine tumors (22). Hereditary and sporadic gastrointestinal carcinoid tumors that are associated with point mutations or deletions of the MEN 1 gene on chromosome 11q 13 tend to be gastrin cell tumors of duodenal or proximal jejunal origin (23). The MEN 1 gene encodes a protein product "menin" that is expressed ubiquitously in endocrine and non-endocrine tissues. Menin exhibits tumor suppressor activity, presumably by modulating histone methylation in promoters of HOX genes and various cyclin-dependent kinase inhibitors. Distal jejunal and ileal carcinoid tumors tend to be associated more specifically with inactivation or losses in chromosomes 18p, 18q, 11q, 16q, and 9p, and to be associated with overexpression of transforming growth factors and , epidermal growth factor, fibroblast growth factor, and neural cell adhesion molecules and their receptors (24, 25).

Adenomas, Epithelial Dysplasia and Adenocarcinoma

In the SEER population, the average annual age-adjusted incidence per 1,000,000, based on the 1973–2005 registration, for adenocarcinoma of the small intestine was 6.8 (white men), 4.5 (white women), 12.2 (black men), and 10.2 (black women). The incidence per 1,000,000 for adenocarcinoma of the colon (excluding rectum) was 447.3 (white men), 345.9 (white women), 498.7 (black men), and 402.6 (black women) (Table 1). Therefore, the ratio of the rates for adenocarcinoma of the colon in white men, when compared with that for adenocarcinoma of the small intestine, was 65.8. Adenocarcinoma composed about 30% to 40% of the total of registered cancers in the small intestine in whites and blacks, respectively, whereas the proportion of total cancers classified as adenocarcinoma in the colon exceeded 98%. The predominant locations in the small intestine for adenocarcinoma are the duodenum and proximal jejunum (Table 2, Fig. 1). The classification of adenocarcinoma of the periampullary region encompasses tumors located in the duodenum, and in the distal common bile and pancreatic ducts. Adenocarcinomas in the duodenal ampulla of Vater may manifest morphologic and biologic features of enteric mucosal or pancreaticobiliary duct epithelium, and are associated with increases in incidence of colorectal adenomas and carcinomas (26, 27). The temporal patterns for the incidence of adenocarcinoma in the small intestine and colon both reflect the higher rates in men compared to women (Figs. 2 and 4) and blacks compared to whites (Figs. 3 and 5). In the survey by Severson et al. (28) that compared average annual rates per 1,000,000 in the SEER database, the incidence of adenocarcinoma of the small intestine increased among black men from 8.2 (1973–1977) to 16.0 (1987–1999), and among white men, the incidence increased from 6.2 to 8.5; among black women, the incidence increased from 5.1 to 15.7, and among white women, from 4.8 to 5.1. In the most recent 5 years of SEER data collection, 2000–2005, the incidence varied slightly among white men from 7.1 in 2000 to 8.9 in 2005, and among black men, from 11.1 to 12.7. Among white women, the incidence varied from 3.9 to 5.4, but among black women, decreased slightly from 11.8 to 10.3. The corresponding annual percentage change increase in the incidence of adenocarcinoma across the 32-year period was lowest among white women (0.9%), 1.4% among white men, 2.4% among black men, and highest among black women (3.0%).

Adenocarcinomas may appear as polypoid, infiltrating, or as annular constricting lesions. As in the colon, the adenoma in the small intestine is a precursor of adenocarcinoma (29). Residual adenomatous tissue is observed commonly at the margins of sporadic carcinomas, and of carcinomas in patients with familial adenomatous polyposis. The spatial distribution of enteric adenomas parallels the distribution of carcinomas in enteric sites (30). In familial adenomatous polyposis, the prevalence of adenomas throughout the duodenum is markedly increased, and the relative risk of adenocarcinoma in the duodenum is increased to more

than 300 times that of a referent population (31, 32). The morphology of enteric adenomas tends to be more villous, or tubulovillous, than the predominant tubular pattern evidenced in the colon. The risk potential for neoplastic transformation of adenomas increases with components of villous histopathology, increasing size in cross-sectional diameter (e.g., 1 cm), and with a higher grade of dysplasia.

Genetic syndromes predisposing to neoplasia in the small intestine are characterized by a familial history, although the type of cancer may appear *de novo* in the absence of a family history, and the associated cancers are generally diagnosed at a younger age than sporadic tumors. Such cancer-associated syndromes may be attributed to a single predominating nucleotide mutation, or to multiple genes on the same or different chromosomes, and are associated with multicentric precursor and neoplastic lesions in other gastrointestinal or other systemic organs (33). The pathogenesis of sporadic invasive adenocarcinoma in the small intestine involves mutational and epigenetic pathways that simulate the multistep events in colorectal neoplasia. Mutations have been reported in adenomatous polyposis coli, β -catenin, E-cadherin, K-ras, p53, and 18q alleles that presumably participate in the adenoma-carcinoma histogenesis pathway (34-36). In studies of adenocarcinoma of the ampulla of Vater, the nuclear accumulation of β -catenin, and K-ras mutations, has been associated with increased cyclin D1 expression (37, 38). Truncating mutations at the adenomatous polyposis coli 5q locus occur infrequently in small intestinal neoplasia, in contrast to their higher prevalence in colorectal adenomas and carcinomas. The truncated adenomatous polyposis coli protein results in aberrations in critical functions of cell adhesion, cell migration, apoptosis, unregulated intracellular accumulation of β -catenin, and the augmented transcription of specific oncogenes such as cMYC and cyclin D1 (39, 40). Losses at chromosome 18q 21-22 would negatively affect growth mediation by transforming growth factor- β signaling (41). Consistent with colorectal cancer, 10% to 15% of cases of adenocarcinomas of the small intestine exhibit high microsatellite instability indicative of DNA mismatch repair dysfunction (42). Most germ line mutations reside at hMLH1 and hMSH2 loci (43). Individuals affected with hereditary nonpolyposis colorectal cancer are at increased risk of developing extra-colonic carcinomas in the small intestine, endometrium, pancreas, renal pelvis, stomach, liver and biliary tract, and ovary, and central nervous system gliomas. The lifetime risk of small intestinal neoplasms in patients with hereditary nonpolyposis colorectal cancer has been estimated to range from 1% to 4% (44, 45). The tumors are located primarily in the duodenum. The tumors that manifest a high level of microsatellite instability tend to have a distinctive phenotype of poor differentiation, prominent lymphocyte infiltration, and mucin production (46). Microsatellites contain a limited number of DNA sequences repeated in tandem and exhibit polymorphisms in length throughout the genome. Because they are repetitive, microsatellites are prone to strand slippage and errors in replication.

A hallmark of the Peutz-Jeghers syndrome is the presence of hamartomatous polyps in the small intestine, colon, and stomach. The syndrome is an autosomal dominant disorder caused by a germ line mutation in the serine/threonine kinase gene, STK11/LKB1, a tumor suppressor gene located on chromosome 19p13.3 (47-49). Most mutations are small deletions, insertions, or base substitutions resulting in an abnormal truncated protein. Another prominent feature is the distribution of melanin pigmented lesions on the lips, perioral region, hands, and buccal mucosa. Patients with the syndrome are at increased risk of small bowel, other gastrointestinal, breast, ovarian, uterine cervical, ovarian, testicular, and lung cancers (50-52).

Non-Hodgkin Lymphomas

The non-Hodgkin lymphomas comprise a broad spectrum of lymphoproliferative neoplasms arising from B cells, T cells, and natural killer cells. Primary lymphomas of the small

intestine include mucosa-associated lymphoid tissue lymphoma, diffuse large B-cell lymphoma, immunoproliferative lymphoma, also classified as immunoproliferative small intestinal disease or IPSID, and enteropathy-associated T-cell lymphoma (EATL). Diffuse large B-cell, immunoblastic, and Burkitt lymphomas arising in the small intestine have been reported in patients with human immunodeficiency virus infection (53). In the SEER population, the average annual age-adjusted incidence per 1,000,000, based on 1973–2005 registration, for non-Hodgkin lymphomas was 4.9 (white men), 3.4 (black men), 2.5 (white women), and 1.5 (black women) (Table 1). The lymphomas accounted for approximately 18% to 23% of enteric neoplasms in whites, and 7% to 11% in blacks. In contrast, non-Hodgkin lymphomas in the colon accounted for less than 1% of all registered neoplasms.

The majority of enteric lymphomas are B-cell lymphomas. The evolution and progression of B-cell lymphomas involves complex interactions of host immune cells to foreign antigens, accompanied by transforming molecular events, such as chromosomal translocations, and constitutive activation of signaling pathways (54, 55). Extranodal lymphomas arising from marginal zone lymphoid tissue are associated with chronic antigenic stimulation by microbial pathogens, e.g., *Helicobacter pylori* (56), *Chlamydia psittaci* (57), *Campylobacter jejuni* (58), hepatitis C virus (59), or autoantigens. The proximal small intestine is the most common site of origin of immunoproliferative Ig heavy chain disease, or mucosa-associated lymphoid tissue-type lymphoma. The prevalence of IPSID is concentrated in the young adult population in the Middle East and North Africa (60, 61). The early histopathology shows a lymphocytic and plasmacytic infiltration in the bowel wall that may evolve into diffuse large B-cell lymphoma. The limited geographic distribution of IPSID and the apparent efficacy of treatment with antimicrobial agents have suggested that chronic infection is causal in an antigen-stimulated lymphoproliferative disease. In this regard, persistent infection with *C. jejuni* has been implicated based on DNA sequencing, fluorescence in situ hybridization and histochemical studies of biopsy specimens (58).

Patients with a history of celiac disease are at increased risk of T-cell and, with lesser frequency, B-cell non-Hodgkin lymphoma, and adenocarcinoma in the small intestine (62, 63). The relative risk of enteropathy-associated T-cell lymphoma in the small intestine is increased approximately 10-to 20-fold in patients with protracted clinical celiac disease (64, 65). Serologic screening using antigliadin and antiendomysial antibody testing, followed by confirmatory endoscopic biopsy, has estimated that the prevalence of celiac disease in Europe and the United States is about 0.5% to 1% (66, 67). Celiac disease is an autoimmune disorder triggered by the ingestion of gluten peptides contained in wheat, rye, and barley. The alcohol-soluble fraction of gluten, namely gliadin, and similar prolamins in rye and barley, are toxic in genetically susceptible individuals (68). Predisposition to gluten sensitivity has been mapped to the HLA-D region on chromosome 6 (69). In patients with celiac disease, the immune reaction to gliadin evokes a chronic inflammatory response concentrated primarily in the mucosa of the proximal small intestine that is manifested by intra-epithelial T-cell lymphocytosis, hyperplasia of crypt epithelium, and villous atrophy (70, 71). The extent of mucosal damage is correlated with serum titers of IgA endomysial antibodies and tissue transglutaminase antibodies. Celiac patients are at increased risk of a wide spectrum of autoimmune disorders, including dermatitis herpetiformis (72-74).

Mesenchymal Tumors

The average annual incidence per 1,000,000 persons of sarcomas of the small intestine in men (2.1) exceeds that in women (1.5). The most commonly occurring sarcoma in the small intestine is the gastrointestinal stromal tumor or GIST. These mesenchymal tumors arise most often in the stomach, but have been diagnosed in the colon, esophagus, mesentery, omentum, and peritoneum (75). Before the use of immunohistochemistry and the demonstration of expression of cell markers such as CD34 and CD117/ KIT, many of these

tumors were misclassified as leiomyosarcomas or neurogenic tumors (76, 77). The cell of origin of GIST neoplasms is the interstitial cell of Cajal, which is interspersed between the circular and longitudinal muscle layers of the gastrointestinal tract, and normally functions within the autonomic nervous system to regulate intestinal motility. The Cajal pleomorphic cell expresses KIT tyrosine kinase receptor (CD117), which on phosphorylation activates downstream signaling pathways (78). Gain-of-function mutations in the KIT proto-oncogene have been shown in more than 90% of GIST tumors (79, 80). Most KIT mutations have originated in somatic cells, however, GIST tumors arising in the small intestine have been reported in patients with type I neurofibromatosis (78).

LIFESTYLE RISK FACTORS

Tobacco and Alcohol

Risk factors such as the regular use of tobacco (81, 82), excessive alcohol consumption and the interaction with folate deficiency (83), obesity (84, 85), and nutrition (86-88) have been studied extensively in patients with colon cancer. In contrast, studies of patients with adenocarcinoma or malignant carcinoid tumors of the small intestine have been constrained because of the rarity and biologic heterogeneity of the major types of tumor. Studies of tobacco and alcohol that were based solely on the review of medical records (9, 89), or on next-of-kin surrogate interviews (90), have not explored the effects of average concentrations of exposure, cumulative lifetime exposures, induction-latency intervals, or dose-response trends. In a population-based study conducted in Europe, Kaerlev et al. (91) reported modest estimates of risk for malignant carcinoid tumor associated with smoking (OR = 1.9; 95% CI = 1.1, 3.2), but no association with adenocarcinoma of the small intestine (92). In a population-based study conducted in Los Angeles County, Wu et al. (93) reported that the odds ratio for smoking cigarettes and adenocarcinoma of the small intestine, after adjusting for use of ethanol, was 2.6 (95% CI = 0.6, 11.6) in men and 1.1 (95% CI = 0.4, 2.7) in women. The estimations of risk were not altered in comparisons of former with current smokers, or in relation to age at starting smoking, number of cigarettes smoked per day, or total years of cigarette smoking.

Consumption of alcohol has also been associated with small bowel adenocarcinomas independently of smoking history (9, 92, 93). In the study by Wu et al. (93) of the consumption of all forms of alcoholic beverages, expressed in grams of ethanol per day, and adjusted for cigarette smoking, the risk of adenocarcinoma was increased 2.9-fold (95% CI = 1.2, 7.1) for patients who consumed more than 80 g (> 6 beverage drinks) per day. Kaerlev et al. (92) found intake of beer and spirits (> 24 g/day), but not wine, was associated with an approximate 3.5-fold increase in risk for adenocarcinoma. The preliminary findings of Chen et al., indicating an association between alcohol intake and carcinoid tumors, have not been replicated (91, 94). Various tumorigenic mechanisms have been attributed to alcohol and its genotoxic metabolite, acetaldehyde, including impaired DNA methylation, inflammation-mediated oxidative stress, and perturbation of the intestinal mucosal immune response (95, 96).

Diet and Body Mass

Dietary factors have been purported to play a role in small intestine neoplasia given that global incidence rates for small and large bowel cancers parallel one another and correlate with per capita consumption of dietary fat and red meat (3, 90). Negri et al. (97) reported an elevated risk of adenocarcinoma of the small intestine among the highest consumers of sugar, refined carbohydrates, and red meat, and a reduced risk associated with higher intake of coffee, fish, fruits, and vegetables (97). Likewise, Chow et al. (90) reported an elevated

risk of dying from small bowel cancer associated with intake of red meat and cured or smoked foods.

Increased body mass is consistently linked to cancer of the colon, yet the few studies examining the relationship between obesity and cancer of the small intestine have produced mixed results (90, 94, 97-100). Wolk et al. (98) observed significant elevation in risk of small bowel cancer among obese men and women (standardized incidence ratio = 2.8; 95% CI = 1.6, 4.5). In a large cohort of U.S. veterans, obesity (body mass index = 30 kg/m²) was associated with an approximate 60% increase in risk of cancer of the small intestine among white men (RR = 1.58; 95% CI = 1.18, 2.12), but not among black men (RR = 1.07; 95% CI = 0.54, 2.08). This risk was further elevated among whites when restricted to duodenal cancers (RR = 2.10; 95% CI = 1.38, 3.22) (99). Similarly, in a Norwegian cohort study of 1,162 cases in 2 million men and women, obese men were 60% more likely to be diagnosed with small bowel cancer (RR = 1.59; 95% CI = 1.13, 2.23) compared to men with normal body mass index (18.5–24.9 kg/m²). However, no relationship between BMI and cancer risk was observed among women, except for cancers of the duodenum (RR = 1.67; 95% CI = 1.00, 2.80) (100). Other studies of obesity and cancer of the small intestine have shown either no association (90) or an inverse relationship with body mass (94, 97).

INTERSECTING PATHOGENIC MECHANISMS

Chronic Inflammation and a Cascade of Cytokines

Chronic inflammatory bowel disease includes two clinically and pathologically distinctive autoimmune entities, Crohn disease (CD) and ulcerative colitis. Crohn disease is a chronic inflammatory condition presenting principally in the distal small intestine, but may involve the colon, mainly the proximal colon, rectum, anus, and perianal tissues, other digestive organs, and tissues outside of the digestive tract. Nearly 50% of patients manifest inflammatory disease that involves both ileum and colon. Focal intestinal inflammation associated with superficial mucosal ulcerations, with segmental distribution or "skip lesions," are early characteristic pathologic features. With increasing chronicity, the ulcerating lesions coalesce and the inflammatory response tends to be transmural and granulomatous (101). The granulomatous inflammation of CD comprises aggregates of macrophages, lymphocytes, plasma cells, and multinucleated giant cells that are formed in response to the release of cytokines such as tumor necrosis factor (102, 103).

The determination of the true incidence of CD is problematic because of the lack of population-based registration data and the difficulty in distinguishing early onset CD from other inflammatory diseases of the small or large intestine. The estimated incidence of CD, ranging from 1 to 15 per 100,000, is highest in North America, northern and western European countries, and in American- or European-born Jews. The incidence of adenocarcinoma in the small or large intestine is increased in patients with CD (104-106). As in ulcerative colitis, the risk of cancer in patients with CD is correlated with early age at onset, duration, and extent of disease in the intestinal organ, and the prevalence of precancerous dysplastic lesions. In population-based studies of patients with CD in the small intestine, the relative risk of carcinoma in the small intestine has been estimated to be increased 10- to 40-fold (107). The cumulative risk at 10 years was estimated as 0.2% (95% CI = 0.0–0.8), and at 25 years, 2.2% (95% CI = 0.7–6.4) (108). In a meta-analysis of six population-based cohort studies, the age-standardized incidence rate ratio for colorectal cancer in patients with CD of the colon was estimated as 2.5 (95% CI = 1.7–3.5) (109).

The integrity of the mucosal barrier lining the intestinal tract, which is maintained by tight junctions between adjacent epithelial cells and relative impermeability of the apical villous brush border, serves an important function in the innate immune system. The intestinal tract

is exposed continuously to commensal indigenous microbial flora and potentially to pathogenic organisms (110). Enteric epithelial cells, in particular Paneth cells secrete antimicrobial substances such as mucus, lysozymes, cysteine-rich defensins, and IgA (111). The constitutive and inducible production of various defensin peptides in the intestinal mucosa limits the invasion and adherence of commensal and pathogenic microorganisms (112). The pathophysiology of CD underscores the pathogenic significance of permeability of the mucosal barrier and of the aberrant immune response by effector lymphocytes and proinflammatory cytokines to indigenous luminal microorganisms or foreign antigens (113-115). The inflammatory response mediated by CD4⁺ Th1-cells is exaggerated and cytotoxic. A salient immunopathogenic mechanism in CD is the resistance of activated T cells to undergo apoptosis (116).

The pathogenesis of CD as shown in animal models and human studies would suggest that protracted intestinal inflammation and its sequelae arise from the interactions of the luminal microflora, immune-mediated tissue injury, and genetic susceptibility (117, 118). Genome-wide linkage analyses have identified 10 suspected loci associated with susceptibility to inflammatory bowel disease (119, 120). The genetic basis for susceptibility to CD is most consistent with a polygenic mode of inheritance (36). A potentially significant gene-phenotype expressed in CD has been linked with at least three variants of the caspase recruitment domain gene positioned at chromosome 16q12 (121). The gene product of caspase recruitment domain 15 is the NOD2 protein, an intracellular receptor for a component of the bacterial cell wall that activates cells of the innate immune system (122). Aberrant NOD2 protein has been shown to result in defective pattern recognition and clearance of invasive bacteria by macrophages and diminished production of microbicidal defensins (123, 124).

As evidenced by the multistep pathogenesis of CD and dysplasia-adenocarcinoma of the small intestine, recurrent or persistent inflammation, whether due to an autoimmune disease or chronic exposure to an infectious or chemical agent, may induce or promote tumorigenesis in a susceptible host and target tissue (125, 126). Phases of cancer promotion and progression are intimately linked to a dysfunctional cytokine network. Cytokines represent a family of biologic response modifiers including interleukins, chemokines, growth factors, and extracellular proteases that interact with cell surface receptors and target genes that influence clonal neoplastic cell proliferation, angiogenesis and migration of tumor cells through the basement membrane and into the stromal matrix (127). In addition, the metabolic products of activated inflammatory cells are accompanied by excessive formation of reactive oxygen and nitrogen species that are potentially damaging to DNA and the integrity of cell surface membranes (128).

Microbial Flora Interacting With Endogenous and Ingested Substrates

In addition to the consideration of the mechanisms linked with chronic inflammation and immune dysfunction, the contrasting incidence of adenocarcinoma of the small and large intestine may be viewed in the context of the differences in microbial density and taxonomy of anaerobic microorganisms in the fecal stream, the enterohepatic metabolism of bile acids and their potential role in tumorigenesis, and rate of intestinal transit. The contents of the fecal stream remain liquid throughout the small intestine. Chyme is transported through the small intestine by peristaltic and segmenting waves, requiring about 3–5 hours for passage from the pylorus to the ileocecal valve. The right colon carries out complex functions that include mixing and fermentation of the ileal effluent, and excretion and desiccation of the intraluminal contents to form stool; the left colon serves as a conduit for desiccation and transport of stool to the rectosigmoid region. Although the rate of transit in the small intestine is correlated directly with the rate of transit in the colon, transit time through the small intestine is generally more rapid per unit length than in the colon and rectum. The

principal points of delay in the large intestine are in the cecum, ascending colon, sigmoid colon, and rectum (129). The electrical rhythm of the small and large intestine is controlled by the enteric nervous system and neuro-hormonal mechanisms, which in turn are modulated by the dendritic and T-cells of the immune system (130). Slowing of the rate of intestinal transit augments the enterohepatic recycling of bile acids, the excreted fecal mass of microorganisms, anaerobic bacterial fermentation of polysaccharides and production of short chain fatty acids, and the rising pH of the fecal stream (131, 132).

A diverse and dynamic microbial ecosystem is normally resident within the lumen or adherent to the mucosal surface of the small and large intestine. The prevalence of microbiota in different anatomic areas of the gastrointestinal tract is influenced by the pH, bowel motility, symbiotic or antagonistic interactions among the various species of microorganisms, mucosal immune mechanisms, oxidation-reduction potential of the luminal contents and mucosa, and nutritional metabolites. Decreased oxidation-reduction potential predisposes to colonization with obligate anaerobic bacteria (132).

The upper two-thirds of the small intestine contain low concentrations of aerophilic Gram-positive bacteria such as *Lactobacilli* and *enterococci*. The density of microbiota increases markedly in the distal ileum, and may contain up to one million anaerobic organisms per gram of luminal contents. The large intestine harbors over 500 species of bacteria, mainly obligate anaerobic Gram-negative and Gram-positive organisms, such as *bacteroides*, *bifidobacteria*, *Clostridia*, and *Enterobacteriaceae* (133). The anaerobic microbial ecosystem in the cecum, at a concentration in excess of one billion bacteria per gram of luminal contents, flourishes because of the relative stagnation of the fecal stream, and the very low oxidation-reduction potential (134). It is of interest that the increased risk of adenocarcinoma in patients with CD occurring in surgically bypassed loops of chronically inflamed ileum has been attributed to stagnation of intestinal contents accompanied by overgrowth of anaerobic bacteria (135).

The enormous number and diversity of microorganisms in the intestinal tract are important in the development of gut-associated lymphoid tissue and immune capacity (136-138). Conversely, the intestinal bacteria provide the metabolic capacity to facilitate xenobiotic transformation and potential synthesis of carcinogenic metabolites. Intestinal anaerobic microorganisms generate various metabolizing enzymes, such as β -glucuronidase, β -glucosidase, sulfatase, nitrate and nitro reductases, and decarboxylases, which act on various substrates such as the bile acids, fatty acids, and steroid molecules. The conversion of ingested chemical agents to genotoxic molecules has been investigated in antibiotic-treated, germ-free rodents. For example, cycasin, found in *Cycadeceae* plants, a methylazoxymethanol glucoside, is not tumorigenic when administered parenterally or orally to germ-free rats. However, when fed orally to rats with normal intestinal microbial flora, less than 50% of the conjugated compound was recovered in the feces and urine, and adenocarcinomas were induced in the large intestine, liver, biliary duct system, and kidney. It was apparent that microbial β -glucosidase had converted cycasin to unconjugated methylazoxymethanol, an active mutagenic and tumorigenic metabolite (139). Similarly, tumor induction by dimethylhydrazine or 2,3-dimethyl 4-aminobiphenyl is enhanced by the β -glucuronidase enzymatic activity of intestinal bacteria (140-142).

Greater than 95% of the bile salts that are synthesized in the liver are reabsorbed either by passive diffusion in the proximal jejunum, or by active transport in the distal ileum. The bile salts are then transported via the portal vein back to the liver where they are absorbed by hepatic cells and again secreted as bile. The enterohepatic recirculation of bile salts recycles about 6–8 times daily (143). The bile salts are the ionized form of the bile acid molecule. The carboxyl group in the side chain of the bile salt molecule when activated can react with

glycine or taurine forming amides known as conjugated bile salts. In glycocholic and glycochenocholic acids, the bile acids are conjugated with glycine, whereas taurocholic and taurochenocholic acids are conjugated with taurine. Intestinal anaerobic bacteria, for example species of the *Bacteroides fragilis* group, deconjugate and dehydroxylate the bile salts by removing glycine and taurine residues and the hydroxyl group at position 7 (144). The primary bile salts are then biochemically transformed into the secondary bile acids, deoxycholic acid and lithocholic acid. The deconjugated and dehydroxylated bile salts are less soluble in intestinal chyme and are therefore less readily absorbed from the intestinal lumen than the bile salts that have not been subjected to bacterial metabolism. Based on both experimental and observational epidemiologic studies, deoxycholic acid has been classified as a potential tumor promoter in conjunction with other genotoxic agents (145-147). Studies of concentration levels of deoxycholic acid in both fecal and serum samples have been associated with colorectal adenomas and cancer (148-150). The relatively prominent distribution of adenocarcinoma in the duodenum and proximal jejunum, particularly after cholecystectomy, has been attributed to proximity to the juncture of the common bile duct (151). Review of physiologic, pathologic, experimental, and epidemiologic studies suggest that the changing microecology, particularly in the colon, is associated with enhanced metabolic activation of ingested and endogenously-formed procarcinogenic substrates.

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Selected Abbreviations and Acronyms

SEER	Surveillance, Epidemiology and End Results
MEN	multiple endocrine neoplasia
GIST	gastrointestinal stromal tumor
CD	Crohn disease

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FIGURE 1.
Age-adjusted incidence rates of adenocarcinoma of the small intestine and colon by cancer site (SEER, 1973–2005).

FIGURE 2.
Age-adjusted incidence rates of adenocarcinoma of the small intestine by gender; all races (SEER, 1973–2005).

FIGURE 3.

Age-adjusted incidence rates of adenocarcinoma of the small intestine by race; all races (SEER, 1973–2005).

FIGURE 4.
Age-adjusted incidence rates of adenocarcinoma of the colon by gender, all races (SEER, 1973–2005).

FIGURE 5. Age-adjusted incidence rates of adenocarcinoma of the colon by race (SEER, 1973–2005).

TABLE 1

Incidence rates and frequency of cancers of the small and large intestine by histology, race, and sex, SEER (1973–2005)

Primary site and histology	Incidence rate (% [*])			
	White men	Black men	White women	Black women
Small intestine				
Adenocarcinoma	6.8 (30.8)	12.2 (37.2)	4.5 (32.7)	10.2 (45.5)
Non-Hodgkin lymphoma	4.9 (22.9)	3.4 (11.4)	2.5 (17.9)	1.5 (7.3)
Carcinoid	7.7 (36.0)	14.4 (43.9)	5.5 (39.2)	8.7 (39.7)
Sarcoma [†]	2.1 (10.3)	2.1 (7.4)	1.5 (10.2)	1.5 (7.5)
Colon				
Adenocarcinoma	447.3 (98.6)	498.7 (98.6)	345.9 (98.7)	402.6 (98.5)
Non-Hodgkin lymphoma	2.9 (0.7)	0.9 (0.2)	1.2 (0.3)	1.0 (0.2)
Carcinoid	2.7 (0.7)	4.7 (1.0)	3.2 (0.9)	4.0 (1.1)
Sarcoma [†]	0.5 (0.1)	0.6 (0.1)	0.3 (0.1)	0.5 (0.1)

Note: Rates are per 1,000,000 and age-adjusted to the 2000 US Std Population (19 age groups – Census P25-1130) standard.

Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 9 Regs Limited-Use, Nov 2007 Sub (1973–2005).

^{*} Percent of histologic groups presented – other histologies not included.

[†] Histologic codes include: 8800–8805, 8810, 8811, 8890–8897, 8930, 8933–8936, 8990–8891, 9044, 9120, 9140, 9180, 9540, 9560, 9755, 9758, 9930.

TABLE 2

Incidence and proportion of cancers of the small intestine by anatomic subsite and histology, SEER (1973–2005)

Anatomic subsite and histology	Rate	Count	%
Duodenum			
Adenocarcinoma	3.0	2,062	58.7
NHL	0.5	340	9.7
Carcinoid	0.8	578	16.5
Sarcoma *	0.3	221	6.3
Other †	0.5	309	8.8
		3,510	100.0
Jejunum			
Adenocarcinoma	1.2	839	42.1
NHL	0.6	446	22.4
Carcinoid	0.4	279	14.0
Sarcoma *	0.4	322	16.2
Other †	0.1	105	5.3
		1,991	100.0
Ileum			
Adenocarcinoma	0.9	603	15.1
NHL	1.0	681	17.1
Carcinoid	3.2	2,282	57.3
Sarcoma *	0.4	264	6.6
Other †	0.2	153	3.8
		3,983	100.0
Other small intestine			
Adenocarcinoma	0.8	576	15.4
NHL	1.4	979	26.1
Carcinoid	2.1	1,471	39.2
Sarcoma *	0.7	501	13.4
Other †	0.3	223	5.9
		3,750	100.0

NHL = non-Hodgkin lymphoma.

Note: Rates are per 1,000,000 and age-adjusted to the 2000 US Std Population (19 age groups – Census P25-1130) standard.

Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 9 Regs Limited-Use, Nov 2007 Sub (1973–2005).

* Histologic codes include: 8800–8805, 8810, 8811, 8890–8897, 8930, 8933–8936, 8990–8891, 9044, 9120, 9140, 9180 9540, 9560, 9755, 9758, 9930.

† Other site includes small intestine (not otherwise specified), Meckel's diverticulum, overlapping segments.